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Brief Clinical Report

Interstitial Deletion of 6q21-q23 Associated With Split Hand

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We report on a 7-month-old boy with interstitial deletion of 6q21-q23 and split-hand defect. He died at 7 months. This is the fifth patient with distal limb anomaly associated with a rearrangement of 6q21 region, and supports previous suggestions that there may be candidate gene(s) for distal limb development in the 6q21 region. Am. J. Med. Genet. 69:268–270, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: interstitial deletion of 6q21-q23; split hand defect; limb malformation

INTRODUCTION

Split hand-split foot (SHSF) is a defect affecting the central rays of the hands and feet. Both cytogenetic [Genuardi et al., 1993] and molecular genetic [Scherer et al., 1994] analyses provided evidence that a SHSF gene is located at 7q21.3-q22.1 region. Additional loci may be at 2q24.2-q31.1 and 6q21 [Palmer et al., 1994]. Four patients with split hand-split foot (SHSF) defect and 6q abnormalities were reported [Viljoen and Smart, 1993; Gurrieri et al., 1995; Pandya et al., 1995]. Of these, 2 had an interstitial deletion of 6q16.2-q23.1 and 6q16.3-q22.3 [Pandya et al., 1995] and the other 2 had a balanced translocation with breakpoint at 6q21 [Viljoen and Smart, 1993; Gurrieri et al., 1995].

We report here an additional case of interstitial deletion of 6q21-q23 associated with a split hand defect.

CLINICAL REPORT

The propositus was the child of a healthy 28-year-old, G2P1 mother and a nonconsanguineous 31-year-old father. Pregnancy was uneventful. He was born at term with a birth weight of 2,650 g. Apgar score at one and 5 minutes was 8 and 9, respectively.

At birth, he had split hand defect between 3rd and 5th fingers of the right hand, camptodactyly of the 2nd, 3rd and 5th fingers and a slender 5th finger of the right hand, and camptodactyly of the 2nd, 3rd and 4th fingers and overlapping fingers of the left fingers (Fig. 1). The nail of the right 5th finger was absent. Roentgenograms of the hands showed central ray defect in the right hand (Fig. 2). The 4th digit and metacarpal were absent, while the thumb, 2nd, 3rd and 5th digits were preserved. The distal phalanx of the 5th digit was absent. He had an apparently low-set, right ear and malformed ears. He also had bilateral cryptorchidism, and posteriorly placed anus. A heart murmur was noted at birth, and echocardiography documented patent ductus arteriosus (PDA) and pulmonary hypertension. Ultrasonography of the brain showed a few cysts around the anterior portion of the left ventricle. Chromosome analysis demonstrated a 46, XY,del(6)(q21q23) (high-resolution, G-banded) (Fig. 3). The parents and a 1 8/12-year-old elder sister of the propositus were phenotypically normal. The chromosomes of the parents were normal.

At 22 days he developed intercostal and sternal retractions, cyanosis and apneic attacks and was intubated for 5 days. At 57 days, he was re-intubated because of apneic attacks. At age 70 days tracheostomy was performed because of frequent apneic attacks. At 4 months he developed seizures and was treated with anticonvulsants. EEG showed high slow waves predominant in the left occipital region. Brain CT and magnetic resonance imaging showed brain "atrophy". Echocardiography documented PDA. He was discharged at age 6 months. He died at home of unknown cause one week after discharge. Autopsy was not performed.

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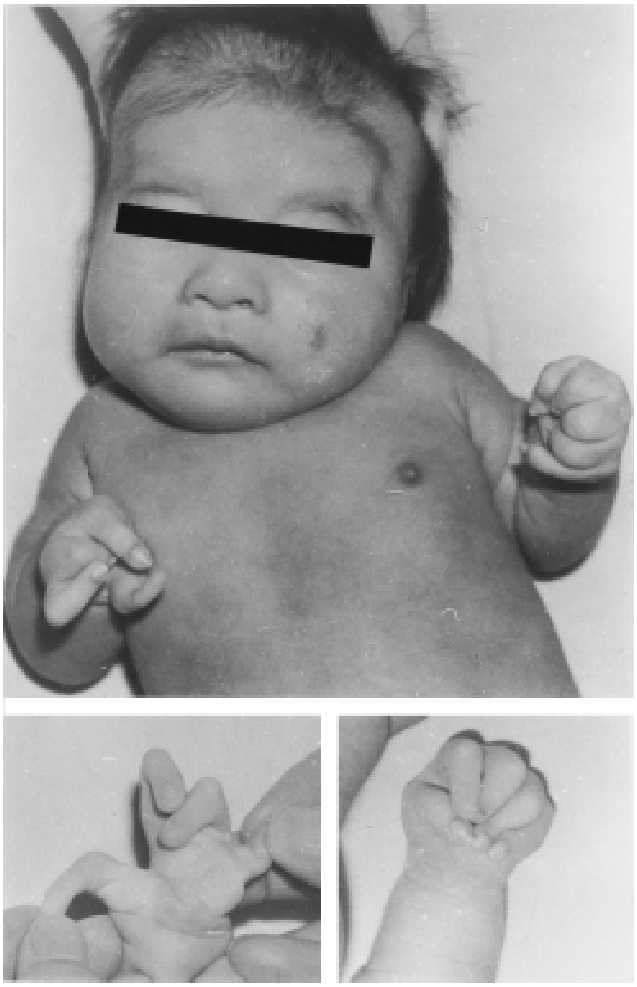

Fig. 1. The patient showing split hand defect of the right hand.

Fig. 2. Roentgenogram of the right hand showing absence of the 4th digit and metacarpal.

DISCUSSION

Patients with interstitial deletion of 6q2 have a distinct phenotype of growth retardation, developmental delay, microcephaly, facial anomalies, sparse hair, congenital heart defects, and variable hand malformations including split hand defect [Pandya et al., 1995]. Of these, growth retardation, developmental delay, microcephaly, and congenital heart defects seem to be nonspecific findings common to autosomal aneuploidy resulting from chromosomal imbalance itself [Lurie and Opitz, 1995]. On the other hand, split hand defect found in our patient is unique and seems to be a more specific finding for interstitial deletion of 6q2.

Several candidate genes for human limb-development defects are known [Roberts and Tabin, 1994]. They include *Msx1* (4p16.1), *Msx2* (5q34-q35), *FGF4* (11q13), *BMP2* (20p2), *BMP4* (14), *Hoxa* (7p14-p21), and *Hoxd* (2q31-q37). In addition, several chromosomal regions in which no candidate genes have been identified are also associated with SHSF defect, including the 7q21.3-q22.1, 2q24.2-q31.1, and 6q21 regions. Palmer et al. [1994] designated the 7q21.3-q22.1 locus as SHSF1 [Genuardi et al., 1993; Scherer et al., 1994], and the second autosomal locus as SHSF2. Thus, the SHSF2 includes 2q24.2-q31.1 [Boles et al., 1993] and 6q21. To our knowledge, 4 patients with split hand or split foot anomaly associated with abnormalities of chromosome 6q21 have been reported (Table I). Hand malformations in these patients were variable. Viljoen and Smart [1993] reported a 44-year-old woman with

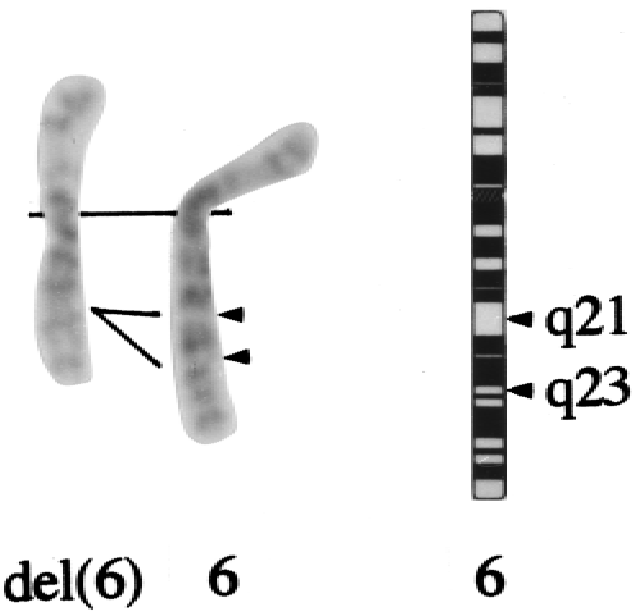

Fig. 3. Partial karyotype showing del(6)(q21q23). Arrowheads indicate breakpoints.

TABLE I. Rearrangement of 6q21 and Limb Anomalies

	Rearrangement	Limb anomalies
Viljoen and Smart [1993]	t(6;13) (q21;q12)	Fingerized thumbs "Lobster-claw" malformation of both feet (bilateral absence of 2nd, 3rd, and 4th digits)
Gurrieri et al. [1995]	t(6;7) (q21;q31.2)	Short forearms Bilateral ulnar ray defects (bowed radii; absent ulnae; presence of the first 3 digits on the left hand with complete 2–3 syndactyly and of the first 2 on the right one)
Pandya et al. [1995]		
Case 1	del (6) (q16.2q23.1)	Bilateral ulnar and radial ray defects (hypoplastic, and functionless 5th fingers; narrow, but well-formed thumb; nonopposable 2nd finger; absence of 3rd and 4th digits bilaterally; absence of 4th and 5th metacarpals) Hypoplastic nails of the postaxial fingers and toes; hypoplastic 4th toes and narrow feet
Case 2	del (6) (q16.3q22.3)	Central ray defect in the right hand (absence of 4th and 5th digits; preservation of functional thumb, 2nd and 3rd digits) Polydactyly in the left hand (six digits including an extra central digit; syndactyly between 5th and 6th digits)
Present case	del (6) (q21q23)	Central ray defect in the right hand (absence of 4th digit, 4th metacarpal, and the distal phalanx of 5th digit, and metacarpal preservation of the thumb, 2nd, 3rd, and 5th digits)

split-foot anomaly, cleft-lip and cleft-palate associated with a 6q21;13q12 translocation. Gurrieri et al. [1995] reported bilateral ulnar aplasia with postaxial oligodactyly in an infant with a 6q21;7q31.2 translocation and suggested that genes in 6q21 may play a role in distal limb development. Pandya et al. [1995] also reported 2 unrelated children with interstitial deletion of 6q, one with breakpoints of 6q16.2q23.1 and the other with 6q16.3q22.3. They had split hand anomalies. The authors indicated from the literature review that these limb anomalies are frequently associated with interstitial deletion of 6q, and suggested 6q2 region as a candidate for the gene(s) involving distal limb morphogenesis. Although gene(s) involving in limb morphogenesis have not been reported in 6q21 region, they suggested that connexin gene (CX43), a gap junction protein gene, which was mapped to human 6q14-q24 region [Laird et al., 1992] is a candidate gene for the limb development. The phenotypic variability among these 4 reported cases may reflect difference in epigenetic expression of gene(s) rather than the difference in gene(s) involved.

The present case supports the previous reports suggesting 6q21 region as a candidate for the gene(s) for limb development. The discovery of candidate genes in 6q21 region for limb development and further study on the function of such genes will provide a deep understanding of their regulation during the limb development.

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ADDENDUM

After this paper was submitted for publication, Gurrieri et al. [Am J Med Genet 62:427–436, 1996] reported a second autosomal SHSF locus to 10q24-q25.

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